Commentary

Role of regulatory T cells in experimental arthritis and implications for clinical use

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Abstract

CD4+ CD25+ T regulatory cells are avidly studied because they modulate immune responses. Their possible role in autoimmunity and more specifically in rheumatoid arthritis (RA) has been highlighted by a string of reports, one of which is in the last issue of *Arthritis Research & Therapy*. There are, however, key questions that have not yet been addressed before their use can be considered as a real therapeutic option. The first is the actual, in a clinical setting, efficacy of Treg to treat active chronic autoimmune diseases such as RA. The second is how we can practically deliver their therapeutic activity in patients. Once these points have been addressed we will have a new and potentially very effective 'magic bullet' for the treatment of chronic autoimmune diseases.

In recent years the T-regulatory (CD4+CD25+ Treg) storm has remodelled the immunology landscape. Since the original reports of a suppressive activity of CD4+CD25+ Treg, in the mid-1980s, an exponential number of papers have appeared in the literature. The employment of CD4+CD25+ Treg for therapeutic purposes is now one of the 'holy grails' in immunology and much effort is focused on the exploitation of this therapeutic avenue. In the last issue of *Arthritis Research & Therapy*, Frey and colleagues [1] provide an additional piece to the CD4+CD25+ Treg jigsaw. In most autoimmune diseases (in humans or in animal models) Treg have been identified [2,3]. In all tested models these cells were capable of preventing or partly inhibiting the induction of an autoimmune response. The absence of Treg, either due to a Foxp3 genetic defect such as that in patients with IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) [4] or scurfy mice [5] or by means of depletion with anti-CD25 monoclonal antibodies in animal models, favours the initiation of a variety of autoimmune diseases [3]. Conversely, the adoptive transfer of CD4+CD25+ T cells prevents the induction of autoimmune responses [3]. The important role of CD4+CD25+ Treg during the induction phase of autoimmunity has also been previously confirmed in collagen-induced arthritis [6], one of the most widely used RA animal models [7].

Frey and colleagues [1] show that CD4+CD25+ Treg also have a fundamental role in the experimental antigen-induced arthritis. However, not all RA animal models seem to respond to CD4+CD25+ Treg manipulation as described in proteoglycan-induced arthritis [8]. On this backdrop the paper by Frey and colleagues represents only a minor blink of an eye in the vast Treg literature, but Frey and colleagues introduce a provocative 'spin' to their results as they question the potential of the 'therapeutic' role of Treg on established autoimmune diseases. In this model, adoptive transfer of preactivated CD4+CD25+ Treg can prevent the induction of autoimmunity but cannot 'cure' animals with ongoing autoimmunity. Thus it seems that the thresholds to control induction or progression (therapeutic action) of an autoimmune process, by non-antigen-specific CD4+CD25+ T cells, are significantly different. Frey and colleagues also monitored the 'homing' of the CD4+CD25+ Treg and detected an accumulation in the inflamed joints, thus excluding the possibility that the lack of therapeutic activity was due to the inability of CD4+CD25+ Treg to migrate into the inflamed tissue. The authors also pointed out that a 'true' curative activity of CD4+CD25+ Treg has been reported only in colitis animal models [9,10], although it could be argued that experiments in an animal model of type 1 diabetes (T1D) might also be considered curative [11].

What implications might this study have for autoimmune diseases, and specifically for RA? A first message is that when studying CD4+CD25+ Treg we have to bear in mind the compartment (tissue) that Treg are obtained from. Indeed, it is apparent that, to gain significant results, studies on

RA = rheumatoid arthritis; T1D = type 1 diabetes; TNF = tumour necrosis factor; Treg = regulatory T cell(s).

$CD4^+CD25^+$ Treg should seek to investigate cells from the inflamed tissue or the regional lymph nodes. A series of reports in animal models of autoimmune diseases, such as T1D [11,12], and also in cancer [13], have clearly demonstrated this point. This indicates that it might be meaningless to monitor peripheral levels of $CD4^+CD25^+$ Treg. However, in humans there are obvious restrictions because access to the inflamed tissues or regional lymph nodes is often impracticable. The present study also indicates that, despite the localized accumulation at the site of inflammation, $CD4^+CD25^+$ Treg might not be sufficient to suppress an ongoing chronic autoimmune inflammatory process.

This idea had already been hinted at by a series of studies in RA and other chronic autoimmune joint inflammatory diseases such as juvenile idiopathic arthritis and spondyloarthropathies, in which phenotype, distribution and functional studies of $CD4^+CD25^+$ Treg have been performed [14–17]. In all these studies $CD4^+CD25^+$ Treg were detected in the joints or synovial fluid of the patients. In these reports it was also shown that the identified $CD4^+CD25^+$ Treg had a suppressive function and accumulated in the inflamed joint [14–17]. One of these studies even reported that $CD4^+CD25^+$ Treg isolated from joints of patients with active arthritis had a more powerful suppressor activity than peripheral $CD4^+CD25^+$ Treg [17]. Thus, despite the presence of an increased number of $CD4^+CD25^+$ Treg with a powerful suppressor activity, RA is not suppressed but the disease is instead very active. The authors provided a startling explanation for this apparent incongruence, in their discovery that tissue-infiltrating effector (pathogenic) T cells were less prone to be 'suppressed' by $CD4^+CD25^+$ Treg than resting or naive peripheral blood T lymphocytes [17]. This study therefore suggested that during a chronic autoimmune inflammatory disease $CD4^+CD25^+$ Treg are attracted to and accumulate where needed but fail to suppress the autoimmune inflammation. These results therefore further indicate, in keeping with the paper by Frey and colleagues, that therapeutic use of $CD4^+CD25$ Treg might not be a feasible option.

However, a recent study has proposed that anti-tumour necrosis factor (TNF)-α, a benchmark therapy for RA, drastically influences the function of $CD4^+CD25^+$ Treg [18]. The crucial point of that study was that Treg isolated from patients with active RA before treatment with anti-TNF-α were unable to suppress proinflammatory cytokine secretion from activated T cells and monocytes. After anti-TNF-α treatment the 'hibernated' peripheral blood $CD4^+CD25^+$ Treg pool recovered and powerfully inhibited, as in healthy controls, not only T cell proliferation but also the production of TNF-α and interferon-γ [18]. However, the presence of functionally efficient peripheral $CD4^+CD25^+$ Treg after anti-TNF-α therapy might be due to a simple redistribution of these cells, which accumulate in the joints during the active phase of RA. It is indeed well known that anti-TNF-α treatment decreases the infiltrate in joints. Furthermore, RA patients relapse shortly after withdrawal of anti-TNF-α [19] and thus, despite the dampening of joint inflammation and the reinstatement of fully functional $CD4^+CD25^+$ Treg, RA is still not cured. These strands of evidence seem to play down a hypothetical therapeutic role of $CD4^+CD25^+$ Treg in RA.

Are there further possible avenues to be explored in the area of $CD4^+CD25^+$ Treg? One possibility is to investigate the use of antigen-specific $CD4^+CD25^+$ Treg. Indeed, it has been reported that antigen-specific $CD4^+CD25$ Treg, generated and expanded *in vitro*, might tip the balance and allow a true curative action in animal models of T1D [12], and much work is now directed to this area [20]. Two recent studies in T1D and experimental autoimmune encephalomyelitis have highlighted the potential of this option by genetic manipulation of T cells [21,22]. However, this might not be an easy road to follow in humans because not all autoantigen-specific T cells seem to be effective in treating an ongoing autoimmune disease as described in the T1D model [22]. Therefore in humans such a prescreening of effective genetically redirected autoantigen-specific T cells might be a highly complex task that is not always easy to achieve. However, in this context, recent studies on RA have indicated that antigen-specific (HC-gp39) $CD4^+CD25^+$ Treg might be deficient in patients in comparison with controls [23]. A more recent study indicated that in a restricted group of RA patients orally challenged with dnaJP1 (a peptide derived from a bacterial heath shock protein) an increase in $CD4^+$ $CD25^+$ Treg was induced, with evidence of a shift from a proinflammatory profile to a potentially regulatory one [24]. Although both studies focused on peripheral blood T cells, they provide encouraging new avenues for novel therapeutic strategies in RA. Still, more work is required to establish whether harnessing $CD4^+CD25^+$ Treg will represent a viable therapy for RA and other autoimmune diseases in the future.

Competing interests

The author(s) declare that they have no competing interests.

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